Innovative multicomponent reactions and their use in medicinal chemistry

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CHAPTER 4

SYNTHESIS OF HIGHLY SUBSTITUTED IMIDAZOLE URACIL CONTAINING MOLECULES VIA THE UGI-4CR AND PASSERINI-3CR

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ABSTRACT

The synthesis of Uracil containing tetra/tri-substituted imidazoles was demonstrated using Ugi/ Passerini-reaction followed by post-cyclization reaction sequence. The approach enables the facile construction of diverse compounds in moderate to excellent yield (47-82%) in one-pot. These scaffolds are currently produced to fill the screening deck of the European Lead Factory.

INTRODUCTION

Uracil **(I)** together with thymine and cytosine constitute a set of pyrimidine nucleobases which are present in all living systems as the components of nucleic acids.[1] Many uracil derivatives are chemotherapeutics with a unique broad spectrum of activities, for example 5-fluorouracil **(II)** and 5-mercaptouracil **(III)** are important anticancer agents, widely used in oncology [2-3] by inhibiting the activity of thymidylate synthase. N1-Substitution of the uracil ring with a sugar or an acyclic moiety is very often related with antiviral and anticancer activity of the related compounds. Idoxuridine **(IV)**, an inhibitor of DNA polymerase, is used in the treatment of Herpes simplex virus infections.[4] Retrovir **(V)**, an inhibitor of HIV reverse transcriptase, was introduced to clinical use in 1987 as the great breakthrough in anti-HIV therapy.[5] Furthermore Sofosbuvir **(VI)** was recently approved as a medication for the treatment of hepatitis C.[6] The introduction of additional structural subunits on the uracil ring frequently changes the molecular target. The ability to modify individual nucleobases is of major importance both for the development of drugs[7] and the study of nucleic acid function and structure.[8] The functionalization of uracil and related nucleobase derivatives has been extensively investigated, as these systems represent core structural elements for a broad variety of pharmaceutically active compounds.[9]

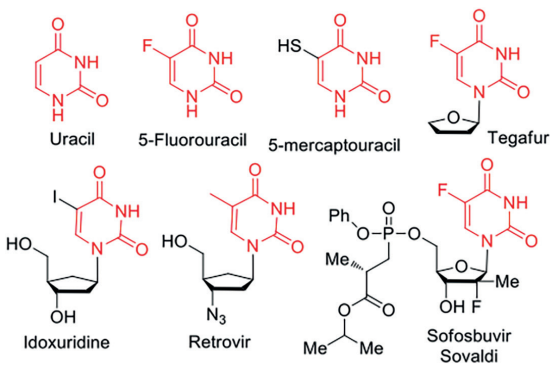


Figure 1. Uracil and Uracil containing drugs.

Apart from uracil, the imidazole moiety is also important and plays a critical role in biology as it forms hydrogen bonds with drugs and proteins.[10] It is found in several important natural products, including purine, histamine, histidine and nucleic acids. Moreover, imidazole derivatives have a wide range of catalytic properties and became popular as *N*-heterocyclic carbines (NHC) in organocatalysis.[11] The vast majority of the synthetic routes towards imidazole synthesis focuses on the synthesis of disubstituted imidazole rings.[13] The Van Leusen three component imidazole synthesis (vL-3CR) is a common and convenient synthetic strategy, however is limited to tosylmethyl isocyanide (TosMIC) or its derivatives.[12] In recent years there has been a tremendous development in literature for disubstituted imidazoles via multistep ring closing methods which are limited in scope and require harsh conditions.[13] However, synthesizing tri- and tetra-substituted imidazoles with a specific substitution pattern can be challenging. Importantly, uracil containing, tetra-substituted imidazoles are particularly difficult to obtain.

In this context, multi component reactions (MCRs) are recognized as valuable tools to decorate the complex molecules in short and mild process, particularly isocyanide based multicomponent reactions (IMCRs) (Ugi- and Passerini) are highly convergent processes which have a great impact in pharmaceutical and drug discovery research.[14] Hence, the synthesis of imidazole rings by Ugi and Passerini reactions could be an interesting subject to study and explore through IMCRs.

RESULTS AND DISCUSSION

As part of ongoing research in our laboratory on IMCRs for the synthesis of heterocycles we report the synthesis of highly substituted uracil containing imidazoles through the Ugi and Passerini reactions followed by cyclization with ammonia. [15]

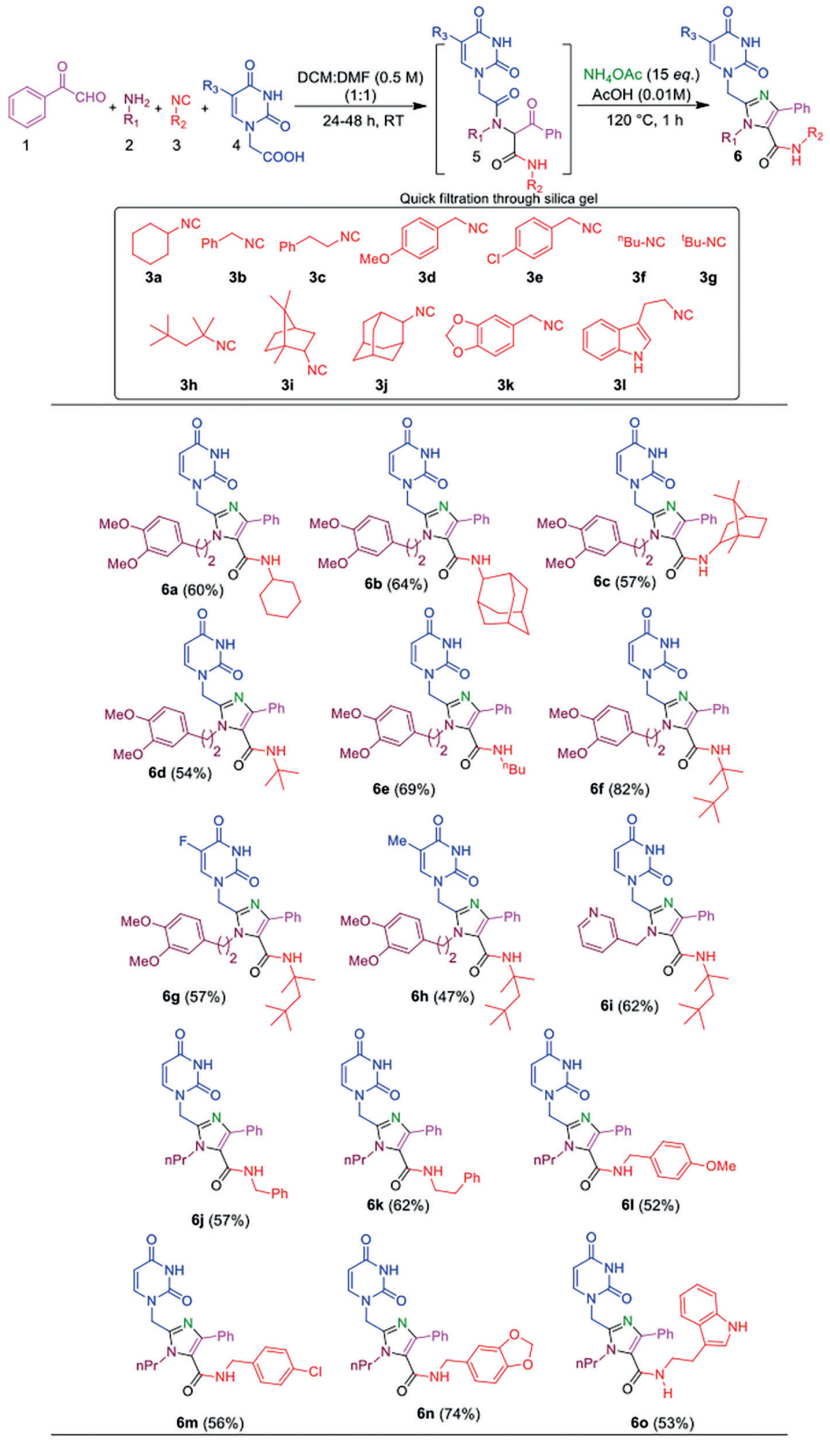
Initially, the Ugi four-component reaction (U-4CR) of phenylglyoxal, 3,4-dimethoxyphenethylamine, cyclohexyl isocyanide and uracil derived acetic acid in methanol (1 M) furnished the corresponding product in poor yields after 48 h. When we performed the U-4CR with solvents like DCM, THF, CH_3CN, H_2O and MeOH, we obtained either low yield or no reaction at all, even with longer reaction times (due to the solubility of the uracil acid). To overcome this problem, we screened different combinations of solvents like DCM/MeOH and CH_3CN/MeOH. After thorough investigation we found that DCM/DMF (1:1) solvent system is the optimum solvent mixture for this Ugi-reaction to yield up to 90% within 48 h. After completion of the Ugi reaction we tried to convert the Ugi products to the corresponding imidazoles in toluene by treating with NH_4OAc and convetional heating at 120 °C for 4 h, but we obtained low yield of the targeted imidazole compounds. Then we shifted to MW-assisted chemistry. After quite some optimization, we found the combination of acetic acid with NH_4OAc (excess) at 120 °C for 1 h afforded the desired product in 75% yield.

Having this in mind, we performed the U-4CR and the post-cyclization reaction in one pot. The optimized conditions use 1.0 equiv. of isocyanide **3a** relative to the aldehyde 1 (1.0 mmol), amine **2** (1.0 mmol) and **3** (1.0 mmol) in DCM:DMF (1:1 ratio, 1 M) at rt for 48 h. After quick filtration and evaporation of the solvents the resulting crude material was treated with NH_4OAc (15 equiv.) in AcOH (0.5 M) at 120 °C for 1 h furnishing the desired product **6a** in 60% overall yield.

It seems that the isocyanides **3a-l** did not affect the yield of the corresponding imidazoles (Table 1, entries 1-15), without showing any steric hindrance factors. Interestingly, adamantane and camphor derived isocyanides were also valid substrates considering their size. The U-4CR and post cyclization reaction works with all aliphatic and aliphatic-aromatic amines and gave us a variety of tetra substituted imidazoles in good to excellent overall yields (Table 1, entries 1-15). Products **6g** (57%) and **6h** (47%) were obtained from 5-fluorouracil and 5-methyluracil acetic acids respectively.

After the successful synthesis of the tetra-substituted imidazoles, we planned to synthesize a series of substituted oxazoles by employing the Passerini-reaction as an initial step. The above optimized reaction and cyclization conditions proved to be ideal also for the Passerini reaction. Phenylglyoxal, cyclohexyl isocyanide and uracil derived acetic acid were reacted in DMF:DCM (1:1, 1 M) for 48 h. The crude mixtures were treated with NH_4OAc (15 equiv.) in AcOH (0.5 M) at 120 °C for 1 h in the MW.

Table 1. Synthesis of tetra-substituted imidazoles **6**.[a,b]



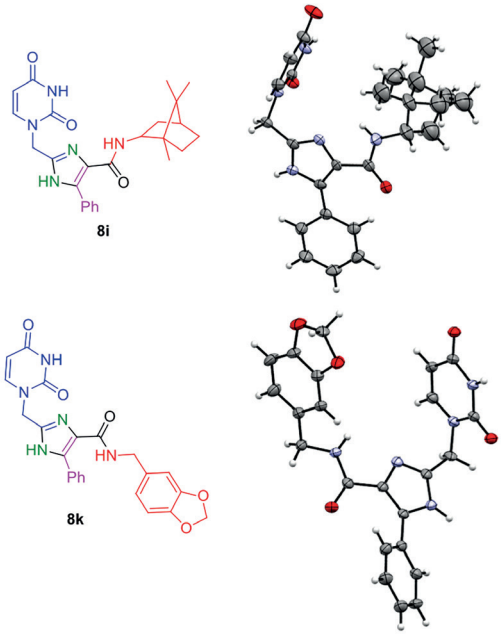
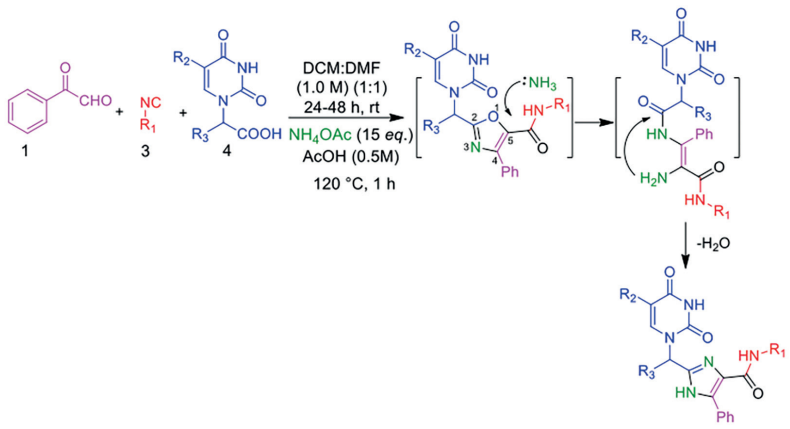


Figure 2. Crystal structures of tri-substituted imidazoles **8i** and **8k**

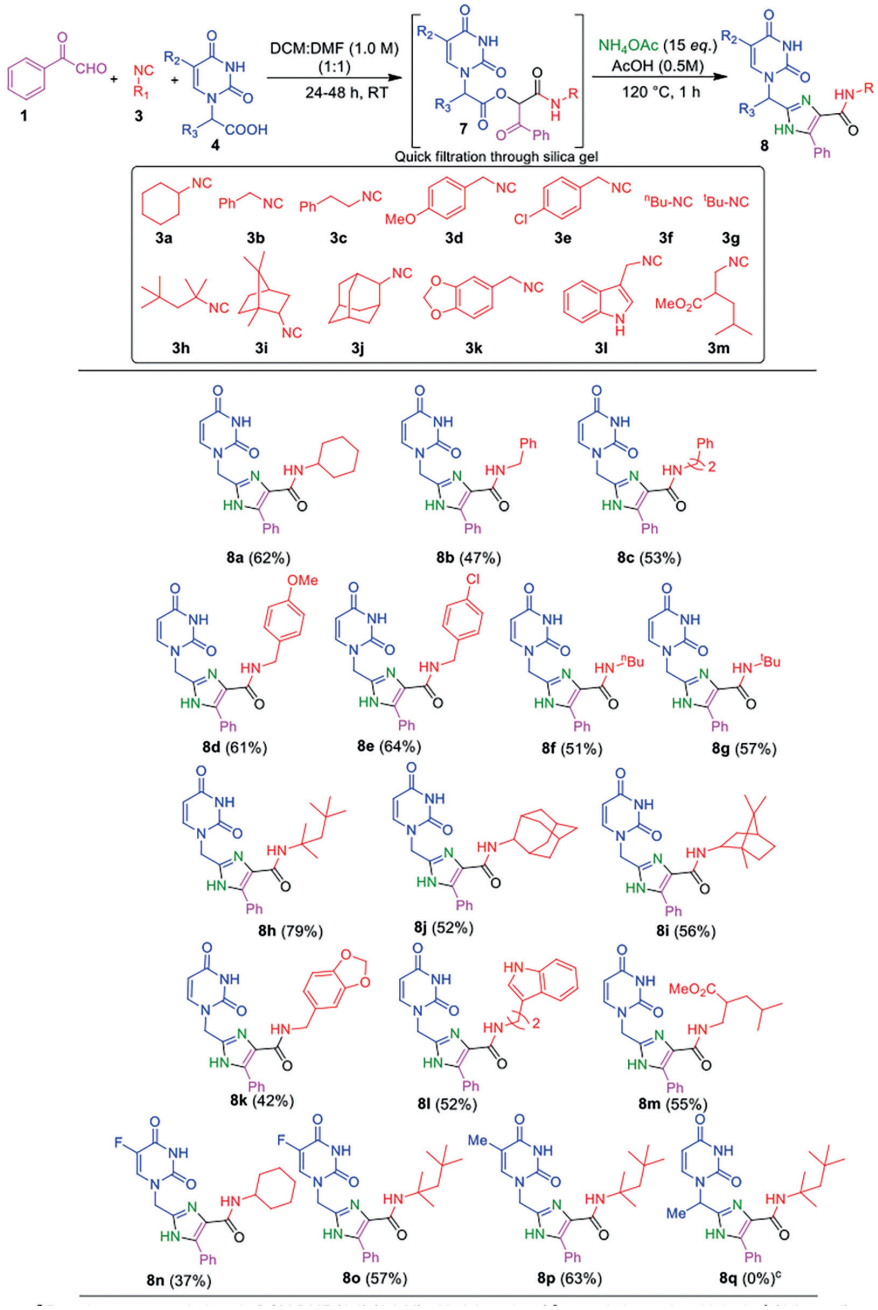
Careful X-ray analysis of compounds **8i** and **8k** showed the formation of a free *NH*-tri substituted imidazole instead of an oxazole.

This is believed to be due to the excess of ammonia involved in the nucleophilic attack at the C5 atom of the formed oxazole, followed by a dehydration step leading to the free NH-imidazoles.



Scheme 1. Proposed reaction mechanism for free *NH*-imidazole formation.

Table 2. Synthesis of tri-substituted imidazoles **8**.[a,b]



With these results in hand we decided to continue for the synthesis of free *NH*-imidazole library. In general, imidazoles were obtained in good yields regardless of their steric and electronic properties. Firstly, a wide variety of aliphatic and aliphatic-aromatic isocyanides (**3a**-**3k**) reacted with phenylglyoxal **1** and uracil derived acetic acid in DCM:DMF (1:1) followed by excess ammonia treatment in AcOH at 120 °C for 1 h furnishing the desired free *NH*-imidazoles **8a**-**k** in very good yield. On the other hand, indole and amino acid derived isocyanides are also valid substrates in the Passerini/cyclization substrates **8l** and **8m**. 5-Fluoro and 5-methyl uracil acetic acids along with phenylglyoxal and different isocyanides furnished the expected tri-substituted imidazoles **8n**, **8o** and **8p** in 37%, 57% and 63% yields respectively.

Imidazole rings are the second most common aromatic nitrogen containing heterocycles amongst U.S. FDA approved drugs.[16a] Nowadays, the imidazole ring is considered as an attractive isostere of triazoles, oxazoles, pyrazoles, thiazoles and tetrazoles, due to its capability to coordinate with a variety of inorganic metal ions as well as biological molecules in the human body. In this report, along with the imidazole ring we have an attractive extra uracil part and based on the excellent scaffold properties these uracil containing imidazoles have are now part of the screening decks of the European Lead Factory (ELF).[16b] In summary, we have described a novel method for the synthesis of uracil containing tetra- and tri-substituted imidazoles. This simple and mild procedure is a valuable addition to MCR chemistry and expands its unique scaffold diversity. Work is ongoing to identify valuable biological targets for our compound libraries which will be reported in due course.

REFERENCES

1. Stryer, L. Biochemistry, 3rd ed.; Freeman, New York, **1988**, 677
2. Longley, D. B.; Harkin, D. P.; Johnston, P. G. *Nat Rev Cancer* **2003**, *3*, 330
3. Al Safarjalani, O. N.; Zhou, X. J.; Rais, R. H.; Shi, J. X.; Schinazi, R. F.; Naguib, F. N. M.; el Kouni, M. H. *Cancer Chemoth Pharm* **2005**, *55*, 541
4. Seth, A. K.; Misra, A.; Umrigar, D. *Pharm Dev Technol* **2004**, *9*, 277
5. De Clercq, E. *Nat Rev Microbiol* **2004**, *2*, 704
6. Lawitz, E., Jacobson, I. M., Nelson, D. R., Zeuzem, S., Sulkowski, M. S., Esteban, R., Brainard, D., McNally, J., Symonds, W. T., McHutchison, J. G., Dieterich, D. and Gane, E. *Ann. N.Y. Acad. Sci.* **2015**, *1358*, 56
7. For some recent reviews, see: (a) Simons, C.; Wu, Q. P.; Htar, T. T. *Curr Top Med Chem* **2005**, *5*, 1191 ; (b) Kimura, K.; Bugg, T. D. H. *Nat Prod Rep* **2003**, *20*, 252
8. Kool, E. T. *Chem Rev* **1997**, *97*, 1473
9. (a) Boudet, N.; Knochel, P. *Org Lett.* **2006**, *8*, 3737; (b) Botta, M.; Saladino, R.; Lamba, D.; Nicoletti, R. *Tetrahedron* **1993**, *49*, 6053; (c) Peters, D.; Hornfeldt, A. B.; Gronowitz, S. *J Heterocyclic Chem* **1990**, *27*, 2165; (d) Asakura, J.; Robins, M. J. *J Org Chem* **1990**, *55*, 4928; (e) Newkome, G. R.; Pandler, W. W. *Contemporary Heterocyclic Chemistry*; Wiley: New York, **1982**
10. (a) Jin, Z. *Nat Prod Rep* **2013**, *30*, 869.; (b) Molina, P.; Tarraga, A.; Oton, F. *Org Biomol Chem* **2012**, *10*, 1711; (c) Narasimhan, B.; Sharma, D.; Kumar, P. *Med Chem Res* **2011**, *20*, 1119; (d) Jin, Z. *Nat Prod Rep* **2006**, *23*, 464; (e) Botta, M.; Corelli, F.; Gasparrini, F.; Messina, F.; Mugnaini, C. *J Org Chem* **2000**, *65*, 4736
11. (a) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem Rev* **2015**, *115*, 9307; (b) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485
12. Van Leusen, A. M.; Wildeman, J.; Oldenziel, O. H. *J Org Chem* **1977**, *42*, 1153
13. (a) Pooi, B.; Lee, J.; Choi, K.; Hirao, H.; Hong, S. H. *J Org Chem* **2014**, *79*, 9231; (b) Zuliani, V.; Cocconcelli, G.; Fantini, M.; Ghiron, C.; Rivara, M. *J Org Chem* **2007**, *72*, 4551; (c) Langhammer, I.; Erker, T. *Heterocycles* **2005**, *65*, 1975; (d) Ueno, M.; Togo, H. *Synthesis* **2004**, 2673; (e) Li, B.; Chiu, C. K. F.; Hank, R. F.; Murry, J.; Roth, J.; Tobiassen, H. *Org Process Res Dev* **2002**, *6*, 682; (f) Zhang, P. F.; Chen, Z. C. *Synthesis* **2001**, 2075; (g) Lee, H. B.; Balasubramanian, S. *Org Lett.* **2000**, *2,* 323; (h) Grimmett, M. R. in *Comprehensive Heterocycle Chemistry II*; Katritzky, A. R., Rees, C., Scriven E. F. V., Eds.; Pergamon Press: Elmsford, NY, **1996**; Vol. 3, 77
14. (a) Dömling, A. *Chem Rev* **2006**, *106*, 17; (b) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471; (c) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J* **2000**, *6*, 3321; (d) Dömling, A.; Ugi, I. *Angew Chem Int Edit* **2000**, *39*, 3168
15. (a) Patil, P.; Madhavachary, R.; Kurpiewska, K.; Kalinowska-Tluscik, J.; Dömling, A. *Org Lett.* **2017**, *19*, 642; (b) Chandgude, A. L.; Dömling, A. *Org Lett*. **2016**, *18*, 6396; (c) Abdelraheem, E. M. M.; Kurpiewska, K.; Kalinowska-Tluscik, J.; Dömling, A. *J Org Chem* **2016**, *81*, 8789; (d) Neochoritis, C. G.; Stotani, S.; Mishra, B.; Dömling, A. *Org Lett.* **2015**, *17*, 2002; (e) Patil, P.; Khoury, K.; Herdtweck, E.; Dömling, A. *Org Lett.* **2014**, *16*, 5736
16. (a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J Med Chem* **2014**, *57*, 10257; (b) Mullard, A. *Nat Rev Drug Discov* **2013**, *12*, 173